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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,718	ISMAGILOV ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-15,17,19,21-30,34,36,38-44,49-62 and 75-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11-15,17,19,21-30,34,36,38-44,49-62 and 75-82* is/are rejected.

7)☒ Claim(s) *53-59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on 03/16/09 is acknowledged. Claims 78-82 are added. Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62 and 75-82 are pending in the application and considered on merits.

Response to Amendment

2. In response to the amendment the examiner withdraws objection to claim 76 and rejection under 112, first paragraph, and modifies rejections under 112, second paragraph, and over the prior art is maintained.

Claim Objections

3. Claims 53-59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 53-59 recite the subject matter, which is irrelevant to the subject matter of the parent claim. The method recited in the parent claims is directed toward crystallization, i.e. toward formation of the crystal. Placing the formed crystal in different glassware for further analysis is not relevant to the method of crystallization, since the crystal is already formed by the method recited in the parent claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 2, 6, 7, 25, 38, 40, 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is unclear, since it is not apparent, as to why and how the method steps are performed after the crystal has been formed in the method of the parent claim?

The term "plug-fluids" is still unclear and ambiguous. The examiner suggests replacing it with the term "plug-forming fluids".

From the claims it is not clear, as to whether the plug-fluids are introduced continuously or discontinuously into the channels. The way the plug-fluids are introduced into the channels is an essential feature of the method, because it is important to know, whether the plugs can be formed in any case, or they can be formed only under the condition of a discontinuous introduction of the plug-fluids.

The examiner is still unclear of the term "permeable" recited in claims 6, 7, 38, 40, 44 in relation to liquid-liquid interaction. According to Merriam-Webster's On-line dictionary: "**permeable** - capable of being permeated: penetrable; especially: having pores or openings that permit liquids or gases to pass through <a permeable membrane> <permeable limestone>". It is not apparent, how this definition can be applied to liquids. The examiner believes that the proper term would be "miscible" or "at least partially miscible". Two liquids can be immiscible with each other, but both miscible with water.

From claim 25 it is not apparent, as to what "indexing marker" might be. Is this a compound? What does it index?

Amended claim 49 did not clarify the term "marker", since it is not clear, how the marker in one plug can be the measure of the component in an adjacent plug.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: removing the plugs or crystals from the microchannel and placing them into the capillary tube.

Claim 60 does not appear to recite any active step, since water evaporation is a natural process. Is it meant to claim "wherein water is evaporated from the plugs"?

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. **Claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-82** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl et al. (US 6,409,832) (Weigl) in view of Chayen (J. Cryst. Growth, 1999) and any of Shaw et al. (GB 2,097,692, IDS) (Shaw),

Lemaitre et al. (WO 98/02237, IDS) (Lemaitre) or Torkkeli et al. (Int. Conf. on Sensors and Actuators, 2001, IDS) Torkkeli).

Weigl discloses "protein crystallization in microfluidic structures" with "a protein samples and a solvent solution combined within a microfluidic channel having laminar flow characteristics which forms diffusion zones, providing for a well defined crystallization". Weigl discusses various types of protein crystallization, and emphasizes that microfluidic crystallization is extremely efficient for diffusion-based crystallization:

> "A T-Sensor-like structure, generally indicated at 10, is shown in FIG. 1 to demonstrate the principles of diffusion-based crystallization. A sample 12 containing dissolved protein, and a reagent 14 containing a variety of different solvents and salts, flow together in parallel within a channel 15 of T-Sensor 10. After establishing a laminar flow profile, the flow is significantly slowed or stopped. The various components of both streams 12, 14 will now diffuse into each other at a certain rate, depending on the size of the molecules within these streams, forming diffusion interface zones 16, 18 within channel 15 of device 10. This action establishes a concentration gradient in device 10, which allows for a very well defined crystallization. Solvent molecules from one stream can diffuse into a parallel stream containing a different solvent and particles. The change in solvent properties along diffusion interface zones 16, 18 can then induce crystallization or precipitation. Obviously, it is also possible to apply a temperature gradient to a microchannel, either across the channel or along its flow direction, and affect the precipitation characteristics this way. Microseeding would be another possibility with this device" (col. 11, lines 54-67 and col. 12, lines 1-8). The fluids are introduced with syringes (under controllable pressure) (col. 12, lines 45-67).

Weigl discloses continuous laminar flow with stopping the flow after establishing a laminar flow profile. Weigl does not specifically disclose crystallization in plugs formed by the plug-fluids comprising corresponding components (a crystallization target, a precipitant, etc.).

Chayen teaches "crystallization with oils: a new dimension in macromolecular crystal growth". In particular, Chayen discloses the following:

> "A series of microbatch experiments shown in Fig. 2 demonstrates how the application of oil can determine the contact area between the trial and its supporting vessel, thereby enabling the experimenter to monitor the nucleation and reduce or increase its level at will. The Figure illustrates three situations: (a) illustrates a drop dispensed into oil as performed by the normal microbatch procedure[4]; the drop forms a spherical shape, with just a small part of it touching the floor of the container; (b) represents a drop which has been dispensed directly onto the floor of the vial and then covered by a layer of oil; the drop spreads out and flattens over the floor of the container, occupying a larger area of contact. In Fig. 2c all contact between the solution of a crystallization trial and its supporting vessel is eliminated by suspending a crystallization drop between two oils of different densities: one of higher and the other of lower density than that of water and the common crystallizing agents. The two oils, high-density fluorinated silicone fluid (ρ 1.27 g/cm3, Merck catalogue no. 63026 2C) and low-density polydimethylsiloxane (ρ 0.92

> g/cm3, Merck catalogue no. 63003 4P) are not miscible and the drop, which has a density value between those of the two oils, floats at the interface thereby not touching the container walls [24,25]. *The number of carboxypeptidase G2 (CG2) crystals produced by procedures (a) and (c) is significantly reduced and their size is larger (Fig. 2d) compared with those grown by procedure (b) where the drop has the largest contact area with its vessel* (Fig. 3e). Similar results have been obtained with thaumatin, lysozyme [24,25] and apocrustacyanin C2 [24]" (page 437, right column, page 438, left column).

Thus, Chayen demonstrates advantages of controlling crystallization in a microdroplet suspended in the oil. Weigl in view of Chayen do not specifically disclose that the interface between plug fluids should have a capillary number sufficient to allow a plurality of plugs to form. Shaw, Lemaitre or Torkkeli teach forming plugs for performing microscale reactions by forming interface between two immiscible fluids. The condition that the capillary number is sufficient to allow a plurality of plugs to form is a prerequisite for forming the plugs, and therefore is inherent to Shaw's, Lemaitre's or Torkkeli's method. Shaw's, Lemaitre's or Torkkeli's method comprises mixing of the reagents in the plugs (droplets).

It would have been obvious for a person of ordinary skill in the art to modify Weigl's method of crystallization in microfluidic structures by performing crystallization in plugs instead of during stop-flow, because Chayen expressly demonstrates preferences of microbatch crystallization in droplets suspended in oil, which are similar to plugs separated by an immiscible carrier fluid in microfluidic channels. Performing crystallization is similar to performing reactions, which involve mixing in the droplets, as disclosed by any of Shaw, Lemaitre or Torkkeli, the method of which also inherently comprises a condition that the capillary number is sufficient to allow a plurality of plugs to form. It would have been obvious to have various plug-fluids comprising different components required for performing crystallization in order to form plugs with different composition and obtain a plurality of crystallization conditions for further high-throughput screening; it would have been obvious for a routineer in the art to analyze crystals either directly from the microchannels or by transferring the crystals into conventional vials used for crystallographic analysis, such as X-ray analysis.

Such embodiments as obtaining different concentrations of the crystallization components for high-throughput analysis is well known in the art, with an obvious modification of the instant method by varying the pressure and the flow rates of the plug-fluids.

8. **Claim 23** is rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen and any of Shaw, Lemaitre or Torkkeli, as applied to claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-82 above, and further in view of Bardell et al. (US 2001/0048900 A1) (Bardell).

While Weigl in view of Chayen do not specifically disclose turn in a channel for increasing mixing in the channel, Bardell discloses specifically such turns in channels for increasing mixing of the fluids in the channels, which makes it obvious for a person of ordinary skill in the art to modify Weigl-Chayen's method by introducing turns in channels for increasing the mixing within the plugs.

9. **Claims 49-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen in view of any of Shaw, Lemaitre or Torkkeli, as applied to claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-82 above, and further in view of Pantoliano et al. (US 6,569,631) (Pantoliano).

While Weigl in view of Chayen do not specifically disclose fluorescent marker within one of the plug-fluids, using fluorescent markers for monitoring crystallization of e.g. proteins is disclosed by Pantoliano, which makes it obvious for a person of ordinary skill in the art to utilize this feature for crystallization monitoring in Weigl-Chayen's method.

Response to Arguments

10. Applicant's arguments filed 03/16/09 have been fully considered but they are not persuasive.

Rejection of the claims under 112, first paragraph, is withdrawn.

The examiner modifies rejections under 112, second paragraph. Some issues are resolved by the amendment, while the others are still pending, as clearly described in the rejection. The examiner did not find any application of the term "permeability" to the case of liquid-liquid interaction in Merriam-Webster dictionary, so if the Applicants can provide specific citation for this term, the examiner would appreciate this. For now the examiner considers the term "miscibility" as conventional one. the term "indexing marker" is still unclear, and the "marker" of claim 49 still does not have a clear meaning.

As to the removing the crystal and placing it in different glassware recited in claims 53-59 - these claims are clearly beyond the scope of the method directed toward forming the crystal, and therefore do not recite any further limitation to the parent claim.

As to the rejection of the pending claims over the prior art, the Applicants argue that Weigl teaches both, the laminar flow and the homogenous solution. The examiner is not sure, why forming the plugs, similar to the droplets of Chayen, by the method disclosed by any of Show, Lemaitre or Torkkeli, will prevent homogenous mixing in the droplets, when Chayen performs such homogenous mixing in the droplets? The examiner does not see any teaching away of Weigl from forming homogenous plugs as taught by Chayen and Show, Lemaitre or Torkkeli, which are moving in a laminar flow. Combination of the advantages of the dynamic laminar flow and crystallization in small droplets is obvious from the combined teaching of Weigl and Chayen.

Again, using the flow of droplets instead of continuous liquid in Weigl's method does not seem to teach away from Weigl's disclosure. Shaw, Lemaitre and Torkkeli disclose performing reactions in the droplets, which requires mixing of the reagents. Chayen specifically discloses preferences of having small volumes for the purpose of crystallization, so it appears that combining different conditions of crystallization disclosed by Weigl for the continuous laminar flow with providing small volumes of droplets or plugs separated by the immiscible liquid in the manner disclosed by Chayen leads to advantages of both methods. The advantages come from providing small volumes of fluids for controlled crystallization, as taught by Chayen and Shaw, Lemaitre and Torkkeli and from the flowing, rather than the stationary, system provided by Weigl.

The Applicants further ask, as to why droplets suspended in oil would be similar to plugs formed by plug-fluids in a micrifluidic system. The examiner, in turn, would like to ask the Applicants, as to what is the difference between them? In fact, one plug of the array of plugs surrounded by the carrier fluid, which can be oil, is exactly the same as a droplet suspended in oil. The only difference between them is that the droplets are moving the capillary. As to the requirement for the specific capillary number, it appears that in order for the plugs to be formed the capillary number should be inherent to the system.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Y. Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

4/27/2009